## REMARKS

Claims 19-22, 24, 30-31, and 49-54 are currently pending. Claims 25, 26, 29, and 33-36 have been cancelled without prejudice, and Applicants reserve the right to pursue the subject matter of these claims in this or other applications, for example, divisional or continuation applications. Claims 19, 24, 30, and 31 have been amended. New claims 49-54 have been added. The amendments to claims 19, 24, 30, and 31 and new claims 49-54 do not constitute new matter.

The Examiner has rejected claims 19-22, 25-26, 29-31, and 33-36 under 35 U.S.C. § 103(a) as obvious over Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") and Fujii *et al.* (U.S. Patent No. 6.197.829) ("Fujii"), in view of Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei"), Knight *et al.* (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono *et al.* (Am. J. Respir. Care Med., 1997, 155:1690-1698) ("Iacono 1997").

The Examiner states that Waldrep, Fujii, and Adjei teach "that cyclosporine is old and well known in combination with various pharmaceutical carriers... particularly, aerosol dosage form." The Examiner states that Knight teaches that cyclosporine aerosol dosage may be in powder form, and that Gordon discloses that dry powder is a well known form for pulmonary delivery. The Examiner states that Iacono 1997 teaches a cyclosporine composition for the treatment of graft rejection.

Based upon these disclosures, the Examiner asserts that it would have been *prima facie* obvious to a person of ordinary skill in the art to combine the cited references to reach the present invention. The Examiner reasons that a person of ordinary skill in the art would be motivated to treat patients with an aerosol dosage form of cyclosporine because cyclosporine is

"well known to be useful for organ transplantation patients and [is] known for treating inflammatory disease or immunological mediated conditions." The Examiner asserts that the selection of the specific treatment regimen is a "simple selection from among obvious alternatives," and that optimization of a result effective parameter is within the skill of the ordinary artisan. In addition, the Examiner states that "prophylactic treatment of transplantation patients with cyclosporine would have been obvious to one of ordinary skill in the art," because the references teach that cyclosporine was well known to be useful for both treatment and prevention of graft rejection. The Examiner states that a method known for treating transplantation rejections would reasonably be expected to prevent the development of rejections, either chronic or acute.

The Examiner has further rejected claim 24 under 35 U.S.C. § 103(a) as obvious over Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") and Fuji et al. (U.S. Patent No. 6.197.829) ("Fuji"), in view of Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei"), Knight *et al.* (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono *et al.* (Am. J. Respir. Care Med., 1997, 155:1690-1698) ("Iacono 1997"), and further in view of Armistead *et al.* (U.S. Patent No. 5,665,774) ("Armistead"). The Examiner relies upon the reasoning set forth above, and additionally states that "Armistead et al. teaches that steroid is useful in treating or preventing graft rejection."

Applicant submits that the Examiner has not set forth a *prima facie* case of obviousness, and respectfully request that the rejections be withdrawn and the claims allowed to issue.

**The Examiner Has Not Established *Prima Facie* Obviousness**

Applicant asserts that the Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must: (A) Determine the scope and contents of the prior art; (B) Ascertain the difference between the prior art and the claims in issue; (C) Resolve the level of ordinary skill in the pertinent art; and (D) evaluate evidence of secondary considerations. See MPEP § 2141 citing *Graham v. John Deere Co.*, 381 U.S. 1 (1966).

At the outset, Applicant notes that new claims 49-54 have been added which recite that the first administration occurs within 31 or 10 days of transplantation, and claims 19, 30, and 31 have been amended to recite that administration occurs "prior to the development of symptoms associated with acute transplant rejection." Support for the amendments and the new claims can be found in the specification at, for example, page 11, line 17 to page 12, line 3, and at page 23, Table 1. Claim 19 has also been amended to delete part (ii) of the claim, which has been incorporated into claim 24. Support for these amendments can be found in the specification at, for example, page 12, lines 8-16.

The References Do Not Encompass the Same Scope And Contents As The Claims

Based upon the claims, as amended, Applicant submits that the references cited by the Examiner do not encompass the same scope and contents as the present invention. None of the references disclose the administration of the claimed aerosolized cyclosporine within 31 or within 10 days of transplantation, or prior to the development of symptoms associated with acute transplant rejection. Waldrep, Fujii, Adjei, Knight, Gordon, and Armistead fail to provide any disclosure regarding the timing of cyclosporine administration. Iacono 1997 discloses that from

June 1993 to September 1995, nine consecutive recipients with persistent acute rejection were given aerosolized cyclosporine; "[o]n average, the patients were observed for approximately 1 [year] before the initiation of aerosolized therapy," and the earliest administration disclosed in Iacono 1997 occurs at 91 days after transplantation. See Iacono 1997 at page 1691, lower left column and at page 1692, Table 2, under "Days Post-Tx." None of the references disclose administration prior to the development of symptoms associated with acute transplant rejection. In fact, Iacono 1997 specifically teaches away from administration prior to the development of symptoms, in that the reference is directed to treatment of patients who are already experiencing symptoms of "persistent acute rejection."

In addition, none of the references cited by the Examiner discloses the use of aerosolized cyclosporine formulations to prevent chronic refractory graft rejection. Waldrep, Fujii, Adjei, Knight, Gordon, and Armistead do not provide any disclosure regarding administration. Iacono 1997 is directed towards the treatment of acute graft rejection after symptoms of persistent acute rejection are evident. In addition, Iacono 1997 does not provide any disclosure regarding the prevention of either acute or chronic graft rejection. See Iacono 1997 at, for example, the abstract.

Accordingly, the references cited by the Examiner do not encompass the same scope and content as the present invention, because none of the references cited by the Examiner teaches the limitation that the first administration occurs prior to the development of symptoms associated with acute transplant rejection, nor do they disclose the treatment of chronic refractory graft rejection.

The References Are Not A Known Option

The Examiner states that a "person of ordinary skill in the art would have been motivated to treat the patients of organ transplantation... prior to the development of symptoms associated with transplant rejection... because cyclosporine [is] known to be useful for organ transplantation patients and [is] known for treating inflammatory disease... and [is] particularly known to be delivered through pulmonary delivery." The Examiner also states that a method known for treating transplantation rejections would reasonably be expected to prevent the development of rejections, either chronic or acute.

Applicant asserts that given the level of ordinary skill in the art and the state of the art at the time of filing, modification of the timing of administration would not be a known option within the technical grasp of a person of ordinary skill in the art. See *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). As discussed above, none of the references cited by the Examiner disclose the prevention of acute or chronic graft rejection, but rather the treatment of acute graft rejection after symptoms of persistent acute rejection are evident. Applicant further notes that the mechanism underlying chronic rejection, as opposed to acute rejection, is not known. For example, DeCamp, Jr., N. Engl. J. Med., 2006, 354:191-193 (Exhibit A) ("DeCamp") states:

> Whereas the mechanism of acute rejection in solid-organ transplantation is well understood as an inflammatory response to allo-antigen stimulation mediated by T lymphocytes, neither the triggers nor the mechanisms of chronic rejection are known.

DeCamp at page 192, left column (emphasis added). Thus, DeCamp demonstrates that in 2006, and therefore at the time of filing of the present application, the mechanisms underlying chronic rejection were unknown. Due to the lack of knowledge regarding the mechanisms behind chronic rejection, a person of ordinary skill in the art could not reasonably conclude that modifying the timing of the administration, based upon data regarding treatment of persistent

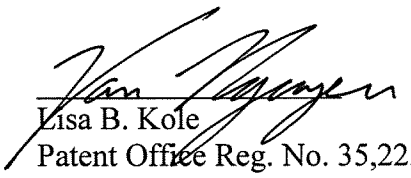
acute graft rejection after it becomes evident, would suggest that pre-symptomatic treatment would be effective in the prevention of chronic refractory graft rejection. Indeed, Iacono 1997 is directed to the treatment of patients who are already experiencing symptoms of "persistent acute" rejection, and therefore teaches away from both administration prior to the development of symptoms associated with acute transplant rejection and administration to prevent chronic refractory graft rejection. Thus, the modification of the timing of administration to prevent chronic graft rejection would not be a "known option within the technical grasp" of a person of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

Based upon the foregoing, Applicant asserts that the present invention is not obvious, and respectfully requests withdrawal of the rejection.

## CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the invention described and defined by claims 19-22, 24, 30-31, and 49-54 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested.

Respectfully submitted,



Lisa B. Kole
Patent Office Reg. No. 35,225

Van H. Nguyen
Patent Office Reg. No. 56,571

Attorneys for Applicant
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112--4498
(212) 408-2500

# EXHIBIT A

the decline in GFR as compared with the results in the control group.[10] This implies that DHCCB therapy sustained glomerular hypertension even though the systemic blood pressure had decreased substantially. Other options to achieve the goal blood pressure and reduce proteinuria have been discussed elsewhere.[5]

Finally, the use of medications to treat other conditions that arise in patients with chronic kidney disease may also help slow the progression of the renal failure itself. For example, there are some data indicating that adding a statin to an ACE inhibitor may enhance the antiproteinuric and renal-protective effects of ACE inhibitors.[11]

The study by Hou et al. does not clarify when in the course of advancing chronic kidney disease should treatment with an ACE inhibitor be stopped. However, common sense mandates that an ACE inhibitor (or an angiotensin-receptor blocker) should certainly be discontinued in the presence of uncontrollable hyperkalemia. Such agents should also be halted to see whether an increase in GFR will ensue, possibly averting the need for dialysis until vascular access is adequate or preemptive kidney transplantation can be performed. By demonstrating that ACE inhibitors can be used successfully in patients with advanced chronic kidney disease, Hou et al. suggest that abandoning treatment with an ACE inhibitor (or angiotensin-receptor blocker) when chronic kidney disease progresses to stage 3 or 4 is not necessary and hastens the onset of end-stage renal disease.

No potential conflict of interest relevant to this article was reported.

From Ohio State University Medical Center, Columbus.

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# Inhaled Cyclosporine — A Breath of Fresh Air?

Malcolm M. DeCamp, Jr., M.D.

During the past two decades, lung transplantation has evolved from a new investigational intervention performed in fewer than 20 patients per year at one institution to an accepted, albeit complex, therapy for a wide variety of end-stage lung diseases that is performed in more than 1700 patients annually at nearly 150 centers worldwide.[1] Early graft failures and deaths of patients were attributable to an amalgam of technical complications, opportunistic infections, and acute rejection. Refinements in surgical technique, enhanced graft preservation, and the routine use of contemporary monitoring and prophylactic and preemptive regimens for opportunistic viruses, fungi, and protozoan organisms have led to improved early survival after lung transplantation (Fig. 1). Newer drugs for the induction and maintenance of immunosuppression have lessened the severity and frequency of acute rejection.[2,3] However, beyond the first year after engraftment, the rate of death among lung-transplant recipients has essentially remained unchanged between the 1980s and the present. At the five-year follow-up, nearly 50 percent of recipients are dead.[1,4]

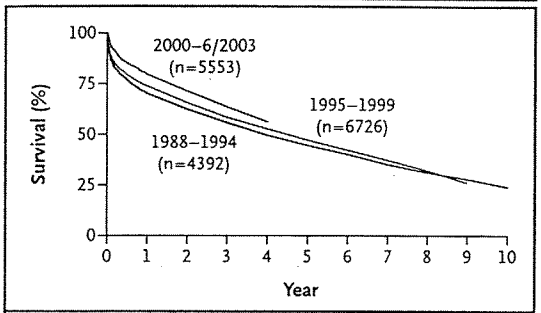


**Figure 1. Differential Kaplan–Meier Analysis of Survival after Lung Transplantation, According to Era, 1988 through 2003.**

Survival declines rapidly in the first year after transplantation. During the past 15 years, improved treatments for both donors and recipients have steadily driven the early-survival curves upward. In contrast, the rate of declining survival beyond the first year (slope of the curves) that is attributable mostly to chronic rejection (obliterative bronchiolitis) remains unchanged in each era. $P=0.01$ for a survival comparison of 1988–1994 with 1995–1999; $P<0.001$ for 1988–1994 as compared with 2000–2003; and $P<0.001$ for 1995–1999 as compared with 2000–2003. The median survival for 1988–1994 was 3.9 years, as compared with 4.5 years for 1995–1999. Data are from Trulock.[1]

Chronic rejection after lung transplantation is recognized histologically as obliterative bronchiolitis and has consistently been the leading cause of death among recipients who survive the first year.[1,5] Whereas the mechanism of acute rejection in solid-organ transplantation is well understood as an inflammatory response to alloantigen stimulation mediated by T lymphocytes, neither the triggers nor the mechanisms of chronic rejection are known. Obliterative bronchiolitis is thought to be the consequence of some combination of immune, ischemic, and infectious injuries. Strategies to limit ischemia, minimize viral infections by matching the cytomegalovirus (CMV) serologic status between donor and recipient, and specific immune therapies to prevent obliterative bronchiolitis have been either impractical or unsuccessful.[6] Moreover, therapeutic interventions short of retransplantation for established obliterative bronchiolitis have been disappointing.[7] In this issue of the *Journal*, Iacono and colleagues provide the first efficacy data from a randomized, placebo-controlled trial of an intervention both to reduce chronic rejection and to enhance survival in lung-transplant recipients.[8] As would be expected, there are some methodologic shortcomings in this small study of an intervention in a complex population of 58 patients, in which randomization cannot hope to balance equally all the confounding variables. Nevertheless, many of these variables would have been expected to negate any benefit of treatment, which makes the results all the more intriguing.

Lung transplantation lags behind other solid-organ transplantation in terms of medium-term and long-term survival. The explanation for this fact is both immunologic and physiological. Because the lung is in direct contact with the environment through respiration, it has a larger lymphocyte mass than do most other transplantable organs. Therefore, lung-transplant recipients usually require higher maintenance levels of immune suppression than do recipients of heart, liver, or kidney transplants.[9,10] This demand produces a clinical conundrum for the lung-transplantation physician in the form of pulmonary infection, since this common consequence of chronic illness is even more common in an immunocompromised host. Unfortunately, dyspnea, cough, hypoxemia, fever, and pulmonary infiltrates are symptoms, signs, and findings associated with both pneumonia and rejection. Lung recipients are the only population of transplant recipients in which most of the serious infectious complications after transplantation occur in the graft itself.

Iacono and his colleagues from Pittsburgh exploited the unique interface of the lung with our world by delivering augmented immune therapy directly to the graft through the airways. They were able to do this without engendering an increase in pulmonary infection and without the risk of detectable systemic absorption and potential nephrotoxicity from larger amounts of calcineurin inhibitors. Previous attempts to achieve this effect with inhaled corticosteroids were unsuccessful.[11] It would appear that inhaled cyclosporine might help in at least delaying the onset of obliterative bronchiolitis and pushing the late-survival curves of lung-transplant recipients upward toward those of heart, liver, and kidney recipients.

The clinical-trials purist will evaluate the study of Iacono and colleagues and see that with regard to the authors' primary end point (the rate of histologic acute rejection), the study must be considered a "negative" trial. Such a perspective, however, places a methodologic tree ahead of the forest. In addition, the trial fell far short of its

prospectively defined accrual goal of 136 patients. Despite generating only 43 percent of the projected study sample, having only 50 percent treatment compliance, and having some substantial imbalances between treatment and placebo groups, there were very few complications of active treatment, and the clinical benefits of the inhaled drug remained statistically significant.

These results should be received enthusiastically by lung-transplant physicians and surgeons but need to be confirmed in a more broadly inclusive multicenter trial. Such trials have been woefully lacking in the lung-transplantation world, in which 78 percent of centers perform fewer than 20 transplantations per year.[1] There is no consensus regionally, nationally, or internationally regarding such important treatment issues as the use of induction immunosuppression, the optimal maintenance combinations of immunosuppressive drugs, strategies for reducing the use of corticosteroids and limiting calcineurin renal toxicity, the question of when to schedule biopsies and when and how to treat acute rejection, and the optimal prophylactic regimen for CMV, pneumocystis, and fungal infections. Lung transplantation remains a low-volume, high-cost intervention. Without a mechanism for sharing experiences, studying new therapies and techniques, and critically analyzing pooled outcomes, the lung-transplantation community will never establish a set of best practices. Instead, it will be doomed to re-create a series of anecdotal experiences. Perhaps the inhaled-cyclosporine story will be that breath of fresh air that brings this community together.

From the Division of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center, Boston.

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